IMMEDIATELY DANGEROUS TO LIFE OR HEALTH (IDLH) VALUE PROFILE

FOR

ETHYLENE DIBROMIDE

[CAS NO. 106-93-4]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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Foreword

Chemicals are a ubiquitous component of the modern workplace. Occupational exposures to chemicals have the potential to adversely affect the health and lives of workers. Acute or short-term exposures to high concentrations of some airborne chemicals have the ability to quickly overwhelm workers, resulting in a spectrum of undesirable health outcomes that may inhibit the ability to escape from the exposure environment (e.g., irritation of the eyes and respiratory tract or cognitive impairment), cause severe irreversible effects (e.g., damage to the respiratory tract or reproductive toxicity), and in extreme cases, cause death. Airborne concentrations of chemicals capable of causing such adverse health effects or of impeding escape from high-risk conditions may arise from a variety of non-routine workplace situations, including special work procedures (e.g., in confined spaces), industrial accidents (e.g., chemical spills or explosions), and chemical releases into the community (e.g., during transportation incidents or other uncontrolled-release scenarios).

The immediately dangerous to life or health (IDLH) air concentration values developed by the National Institute for Occupational Safety and Health (NIOSH) characterize these high-risk exposure concentrations and conditions [NIOSH 2013]. IDLH values are based on a 30-minute exposure duration and have traditionally served as a key component of the decision logic for the selection of respiratory protection devices [NIOSH 2004].

Occupational health professionals have employed these values beyond their initial purpose as a component of the *NIOSH Respirator Selection Logic* to assist in developing risk management plans for non-routine work practices governing operations in high-risk environments (e.g., confined spaces) and the development of emergency preparedness plans.

The approach used to derive IDLH values for high priority chemicals is outlined in the *NIOSH Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health Values* [NIOSH 2013]. CIB 66 provides (1) an update on the scientific basis and risk assessment methodology used to derive IDLH values, (2) the rationale and derivation process for IDLH values, and (3) a demonstration of the derivation of scientifically credible IDLH values using available data resources.

The purpose of this technical report is to present the IDLH value for Ethylene Dibromide (CAS® No. 106-93-4). The scientific basis, toxicologic data, and risk assessment approach used to derive the IDLH value are summarized to ensure transparency and scientific credibility.

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Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AEGLs	Acute Exposure Guideline Levels
AIHA®	American Industrial Hygiene Association
BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower confidence limit
C	ceiling value
°C	degrees Celsius
Ca	Carcinogen
CAS®	Chemical Abstracts Service, a division of the American Chemical Society
CIB	Current Intelligence Bulletin
ERPGs™	Emergency Response Planning Guidelines
°F	degrees Fahrenheit
g	grams
IDLH	immediately dangerous to life or health
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance)
L	Liter
LC	lethal concentration
LC_{50}	median lethal concentration
LCt_{50}	median lethal time
LC_{LO}	lowest concentration that caused death in humans or animals
LEL	lower explosive limit
LOAEL	lowest observed adverse effect level
mg	milligrams
mg/m^3	milligram(s) per cubic meter
min	minutes
ml	milliliters
mmHg	millimeter(s) of mercury
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAEL	no observed adverse effect level
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
ppm	parts per million
RD_{50}	concentration of a chemical in the air that is estimated to cause a 50% decrease in the respiratory rate
REL	recommended exposure limit
STEL	short-term exposure limit
TLV®	Threshold Limit Value
TWA	time-weighted average

UEL	upper explosive limit
WEELs®	Workplace Environmental Exposure Levels

Glossary

Acute exposure: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

Acute Exposure Guideline Levels (AEGLs): Threshold exposure limits for the general public, applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-1, AEGL 2, and AEGL-3 are developed for five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects, ranging from transient, reversible effects to life-threatening effects [NAS 2001]. AEGLs are intended to be guideline levels used during rare events or single once-in-a-lifetime exposures to airborne concentrations of acutely toxic, high-priority chemicals [NAS 2001]. The threshold exposure limits are designed to protect the general population, including the elderly, children, and other potentially sensitive groups that are generally not considered in the development of workplace exposure recommendations (additional information available at http://www.epa.gov/oppt/aegl/).

Acute reference concentration (Acute RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hours or less) of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors (UFs) generally applied to reflect limitations of the data used. Generally used in U.S. EPA noncancer health assessments [U.S. EPA 2018].

Acute toxicity: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hours [U.S. EPA 2018].

Adverse effect: A substance-related biochemical change, functional impairment, or pathologic lesion that affects the performance of an organ or system or alters the ability to respond to additional environmental challenges.

Benchmark dose/concentration (BMD/BMC): A dose or concentration that produces a predetermined change in response rate of an effect (called the benchmark response, or BMR) compared to background [U.S. EPA 2018] (additional information available at http://www.epa.gov/ncea/bmds/).

Benchmark response (BMR): An adverse effect, used to define a benchmark dose from which a reference dose or concentration can be developed. The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments [EPA 2018]..

BMCL: A statistical lower confidence limit on the concentration at the BMC [U.S. EPA 2018].

Bolus exposure: A single, relatively large dose.

Ceiling value ("C"): U.S. term in occupational exposure indicating the airborne concentration of a potentially toxic substance that should never be exceeded in a worker's breathing zone.

Chronic exposure: Repeated exposure for an extended period of time. Typically exposures are more than approximately 10% of life span for humans and >90 days to 2 years for laboratory species.

Critical study: The study that contributes most significantly to the qualitative and quantitative assessment of risk [U.S. EPA 2018].

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism [U.S. EPA 2018].

ECt_{50}: A combination of the effective concentration of a substance in the air and the exposure duration that is predicted to cause an effect in 50% (one half) of the experimental test subjects.

Emergency Response Planning Guidelines (ERPGs™): Maximum airborne concentrations below which nearly all individuals can be exposed without experiencing health effects for 1-hour exposure. ERPGs are presented in a tiered fashion, with health effects ranging from mild or transient to serious, irreversible, or life threatening (depending on the tier). ERPGs are developed by the American Industrial Hygiene Association [AIHA 2016].

Endpoint: An observable or measurable biological event or sign of toxicity, ranging from biomarkers of initial response to gross manifestations of clinical toxicity.

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

Extrapolation: An estimate of the response at a point outside the range of the experimental data, generally through the use of a mathematical model, although qualitative extrapolation may also be conducted. The model may then be used to extrapolate to response levels that cannot be directly observed.

Hazard: A potential source of harm. Hazard is distinguished from risk, which is the probability of harm under specific exposure conditions.

Immediately dangerous to life or health (IDLH) condition: A condition that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment [NIOSH 2004, 2013].

IDLH value: A maximum (airborne concentration) level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted [NIOSH 2004, 2013]. IDLH values are based on a 30-minute exposure duration.

LC_{01}: The statistically determined concentration of a substance in the air that is estimated to cause death in 1% of the test animals.

LC_{50}: The statistically determined concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; median lethal concentration.

LC_{LO}: The lowest lethal concentration of a substance in the air reported to cause death, usually for a small percentage of the test animals.

LD_{50}: The statistically determined lethal dose of a substance that is estimated to cause death in 50% (one half) of the test animals; median lethal concentration.

LD_{LO}: The lowest dose of a substance that causes death, usually for a small percentage of the test animals.

LEL: The minimum concentration of a gas or vapor in air, below which propagation of a flame does not occur in the presence of an ignition source.

Lethality: Pertaining to or causing death; fatal; referring to the deaths resulting from acute toxicity studies. May also be used in lethality threshold to describe the point of sufficient substance concentration to begin to cause death.

Lowest observed adverse effect level (LOAEL): The lowest tested dose or concentration of a substance that has been reported to cause harmful (adverse) health effects in people or animals.

Mode of action: The sequence of significant events and processes that describes how a substance causes a toxic outcome. By contrast, the term *mechanism of action* implies a more detailed understanding on a molecular level.

No observed adverse effect level (NOAEL): The highest tested dose or concentration of a substance that has been reported to cause no harmful (adverse) health effects in people or animals.

Occupational exposure limit (OEL): Workplace exposure recommendations developed by governmental agencies and nongovernmental organizations. OELs are intended to represent the maximum airborne concentrations of a chemical substance below which workplace exposures should not cause adverse health effects. OELs may apply to ceiling limits, STELs, or TWA limits.

Peak concentration: Highest concentration of a substance recorded during a certain period of observation.

Permissible exposure limits (PELs): Occupational exposure limits developed by OSHA (29 CFR 1910.1000) or MSHA (30 CFR 57.5001) for allowable occupational airborne exposure concentrations. PELs are legally enforceable and may be designated as ceiling limits, STELs, or TWA limits.

Point of departure (POD): The point on the dose–response curve from which dose extrapolation is initiated. This point can be the lower bound on dose for an estimated incidence or a change in response level from a concentration-response model (BMC), or it can be a NOAEL or LOAEL for an observed effect selected from a dose evaluated in a health effects or toxicology study.

RD_{50}: The statistically determined concentration of a substance in the air that is estimated to cause a 50% (one half) decrease in the respiratory rate.

Recommended exposure limit (REL): Recommended maximum exposure limit to prevent adverse health effects, based on human and animal studies and established for occupational (up to 10-hour shift, 40-hour week) inhalation exposure by NIOSH. RELs may be designated as ceiling limits, STELs, or TWA limits.

Short-term exposure limit (STEL): A worker's 15-minute time-weighted average exposure concentration that shall not be exceeded at any time during a work day.

Target organ: Organ in which the toxic injury manifests in terms of dysfunction or overt disease.

Threshold Limit Values (TLVs®): Recommended guidelines for occupational exposure to airborne contaminants, published by the American Conference of Governmental Industrial Hygienists (ACGIH®). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is

believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse effects. TLVs may be designated as ceiling limits, STELs, or 8-hr TWA limits.

Time-weighted average (TWA): A worker's 8-hour (or up to 10-hour) time-weighted average exposure concentration that shall not be exceeded during an 8-hour (or up to 10-hour) work shift of a 40-hour week. The average concentration is weighted to take into account the duration of different exposure concentrations.

Toxicity: The degree to which a substance is able to cause an adverse effect on an exposed organism.

Uncertainty factors (UFs): Mathematical adjustments applied to the POD when developing IDLH values. The UFs for IDLH value derivation are determined by considering the study and effect used for the POD, with further modification based on the overall database.

Workplace Environmental Exposure Levels (WEELs®): Exposure levels developed by the American Industrial Hygiene Association (AIHA®) that provide guidance for protecting most workers from adverse health effects related to occupational chemical exposures, expressed as TWA or ceiling limits.

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1.0 Introduction

1.1 Overview of the IDLH Value for Ethylene Dibromide

IDLH Value: 36 ppm (277 mg/m^3)

Basis for IDLH Value: The IDLH value for ethylene dibromide is based on a 45-minute LC_{50} value of 800 ppm in rats [Rowe et al. 1952]. The duration adjusted LC_{50} value for a 30 minute exposure is 1069 ppm. Applying an uncertainty factor of 30 to account for extrapolation from a concentration that is lethal to animals, animal to human differences, and human variability results in an IDLH value of 35.6 ppm (rounded to 36 ppm).

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to ethylene dibromide and (2) the rationale behind the immediately dangerous to life or health (IDLH) value for ethylene dibromide. IDLH values are developed on the basis of scientific rationale and logic outlined in the *NIOSH Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health (IDLH) Values* [NIOSH 2013]. As described in CIB 66, NIOSH performs in-depth literature searches to ensure that all relevant data from human and animal studies with acute exposures to the substance are identified. Information included in CIB 66 on the literature search includes pertinent databases, key terms, and guides for evaluating data quality and relevance for the establishment of an IDLH value. The information that is identified in the in-depth literature search is evaluated with general considerations that include description of studies (i.e., species, study protocol, exposure concentration and duration), health endpoint evaluated, and critical effect levels (e.g., NOAELs, LOAELs, and LC_{50} values). For ethylene dibromide, the in-depth literature search was conducted through January 2018.

1.3 General Substance Information

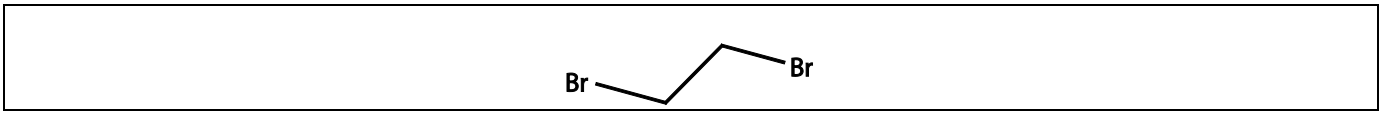
Chemical: Ethylene dibromide

CAS No: 106-93-4

Synonyms[*†]**:** 1,2-Dibromoethane; Dibrom ethylene; dibromoethane; EDB[*]

Chemical category[†]**:** Aliphatic, saturated halogenated hydrocarbons; Organic bromine compounds

Structural formula‡:



References: * NAS [2008], † IFA [2018];‡ NLM [2018]

Table 1 highlights selected physiochemical properties of ethylene dibromide relevant to IDLH conditions. Table 2 provides alternative exposure guidelines for ethylene dibromide. Table 3 summarizes the Acute Exposure Guidelines Level (AEGL) values for ethylene dibromide.

Table 1: Physiochemical Properties of Ethylene Dibromide*

Property	Value
Molecular weight	187.86
Chemical formula	$BrCH_2CH_2Br$
Description	Heavy liquid or colorless liquid
Odor	Sweetish, chloroform like, foul-smelling, pungent
Odor Threshold	Low: 76.8 mg/m^3
UEL	Not flammable
LEL	Not flammable
Vapor pressure	11mmHg@25°C; 17.4 mmHG@30°C
Flash point	Not flammable
Ignition temperature	Not flammable
Solubility	0.43 g/100 ml water; soluble in ethanol and ethyl ether; miscible with most solvents and thinners

*NAS [2008]

Table 2: Alternative Exposure Values for Ethylene Dibromide

Organization	Value
Revised (1994) IDLH value	100 ppm
NIOSH REL[2018]	0.045 ppm, TWA, [Ca]; 0.13 ppm, 15-minute ceil
OSHA PEL [2018a]	20 ppm, TWA; 30 ppm, ceiling; 50 ppm, 5-minute maximum peak
ACGIH® TLV [2017]	Skin; A3 (Not classifiable as human carcinogen)
AIHA® ERPGs™ [2016]	Not available
AIHA® WEELs® [2014]	Not available

Table 3: Interim AEGL Values for Ethylene Dibromide*

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint/ Reference
AEGL-1	52 ppm 400 mg/m^3	26 ppm 200 mg/m^3	17 ppm 131 mg/m^3	7.1 ppm 55 mg/m^3	4.6 ppm 35 mg/m^3	NOAEL for liver toxicity [Rowe 1952]
AEGL-2	73 ppm 562 mg/m^3	37 ppm 285 mg/m^3	24 ppm 185 mg/m^3	10 ppm 77 mg/m^3	6.5 ppm 50 mg/m^3	Slight histopathological changes in the liver; no effect-level for irreversible toxicity [Rowe 1952]
AEGL-3	170 ppm 1,308 mg/m^3	76 ppm 585 mg/m^3	46 ppm 354 mg/m^3	17 ppm 131 mg/m^3	10 ppm 77 mg/m^3	No effect level for lethality [Rowe 1952]

*__Reference__: NAS [2008]

2.0 Human Data

There were two limited reports available regarding human lethality from exposure to ethylene dibromide. Letz et al. [1984] reported death from acute liver and renal failure in two workers exposed via inhalation and dermal contact while working in a tank used to store fertilizer mixtures containing 0.1–0.3% ethylene dibromide. Air samples collected 20 hours after the incident contained 15–41 ppm (average = 28 ppm) in air. The first worker was exposed for approximately 45 minutes and the second worker was exposed for 20-30 minutes, while attempting to rescue the first worker. The first worker collapsed within the first 5 minutes of exposure. Other effects included vomiting, eye and respiratory irritation, central nervous system effects, and diarrhea, resulting in an intermittent comatose state.

Ott et al. [1980] reported that a strong odor and respiratory irritation occurs when ethylene dibromide concentrations reach 75 ppm, and that gastrointestinal discomfort and vomiting may also occur during acute exposure. No other details were reported.

A few studies have evaluated the potential effects of ethylene dibromide on male fertility following occupational exposure [Wong et al. 1979; Ratcliffe et al. 1987; Schrader et al. 1987, 1988]. Though all three of these studies suggested reproductive effects following exposure to ethylene dibromide, it is unclear if these effects would occur as a result of an acute exposure. In addition, these studies reported confounding factors that may have contributed to the reproductive effects observed [Ratcliffe et al. 1987; Schrader et al. 1987, 1988]. These data were not adequate for the derivation of an IDLH value.

3.0 Animal Toxicity Data

Lethality studies on ethylene dibromide are very limited. In a dog study [Merzbach 1929 (as cited in NAS 2008)], one dog for each concentration was exposed to 1, 2, or 5 mL of vaporized ethylene dibromide in a 100 L bell jar for 1 hour. All exposed dogs died, although the one exposed to the lowest concentration died 3 weeks post-exposure. Effects seen at the lowest concentration included signs of restlessness, eye irritation, labored

respiration, and increased respiration rate during exposure. More severe effects, such as lung, heart and liver damage, occurred at higher concentrations.

In the only available acute study conducted according to modern methods, Rowe et al. [1952] exposed groups of four to 30 rats to 100, 200, 400, 800, 1000, 3000, 5000, or 10,000 ppm of ethylene dibromide vapor. Exposure durations ranged from 1.2 minutes to 16 hours. Based on the duration response at each concentration, NIOSH [1977] calculated LCt_{50} values at each concentration. These values can also be interpreted as the LC_{50} at each respective lethal time. The most relevant rat LC_{50} value reported was 800 ppm for a 45-minute exposure. The lowest LC_{50} value was seen in rats exposed to 200 ppm for 12 hours. No rats died after exposure to 400 ppm for 36 minutes. Deaths at the high concentrations were attributed to cardiac and respiratory failure. Deaths seen in groups with <50% mortality occurred several days post-exposure, and were caused by pneumonia secondary to pulmonary damage. Prior to death, effects included weight loss, rough and unkempt appearance, irritability, and bloody discharge from the nose. Increased liver weight and slight histopathologic changes in the liver (not further described) were estimated to be associated with the following concentration/time combinations: 800 ppm for 9 minutes, 200 ppm for 1 hour, and 100 ppm for 4 hours. These liver effects are not escape-impairing or severe, and appear to be reversible; although there is some uncertainty in the absence of additional description of the effects. However, as noted in the next paragraph, there were no liver lesions at 75 ppm in a subchronic study [NTP 1982]. In a repeated exposure study, Nitschke et al. [1980, 1981] reported signs of nose and eye irritation during the first 6-hour exposure to 40 ppm but the severity of these effects were not described. Irritation was not observed at lower concentrations or after repeated exposures. These data were not appropriate for derivation of an IDLH value.

Groups of guinea pigs were also exposed to ethylene dibromide including 20 animals exposed to vapors at 400 ppm for 7 hours, 5 hours, or 2 hours, 10 animals exposed to 400 ppm for 3 hours, and 15 animals exposed to 200 ppm for 7 hours [Rowe 1952]. For the animals exposed to 400 ppm, 20/20 died in the in the 7 hour exposure group, 18/20 died in the 5 hour exposure group, 5/10 died in the 3 hour exposure group. No animals died at the 400 ppm exposure for 2 hours or 200 ppm exposure for 7 hours. Descriptions of clinical signs or necropsy results were not provided [Rowe 1952].

Nasal lesions were reported in rats exposed subchronically to non-lethal concentrations of ethylene dibromide in two studies at concentrations of 15 ppm and higher [Reznik et al. 1980; Nitschke et al. 1980, 1981]. Kidney and liver lesions were not observed in rats or mice exposed to concentrations up to 75 ppm for 6 hours/day, 5 days/week, for 13 weeks [NTP 1982]. NTP [1982] conducted a carcinogenesis assay of ethylene dibromide in rats and mice; neoplasms were reported in the nasal cavity and lungs, blood vessels, adrenal gland, and mammary gland of both species, and the tunica vaginalis in rats. Ethylene dibromide is metabolized to reactive metabolites that bind to DNA, and cause gene mutations and other genotoxicity [NAS 2008]. These data were not appropriate for derivation of an IDLH value.

Table 4 summarizes the most relevant LC data identified in animal studies and provides 30-minute equivalent derived values for ethylene dibromide. Information in this table includes species of test animals, toxicological metrics (i.e., LC, BMCL, NOAEL, LOAEL), adjusted 30-minute concentration, and the justification for the composite uncertainty factors applied to calculate the derived values.

Table 4: Lethal Concentration Data for Ethylene Dibromide

Reference	Species	LC_{50} (ppm)	LC_{Lo} (ppm)	Time (min)	Adjusted 30-min Concentration* (ppm)	Composite Uncertainty Factor‡	30-min Equivalent Derived Value (ppm)†	Final Value (ppm)
Rowe et al. [1952]	Rat	3000	--	10.8	1446	30	48.2	48
Rowe et al. [1952]	Rat	1600	--	18	1111	30	37.0	37
Rowe et al. [1952]§	**Rat**	**800**	--	**45**	**1069**	**30**	**35.6**	**36**
Rowe et al. [1952]	Rat	400	--	120	1077	30	35.9	36
Rowe et al. [1952]	Guinea pig	400	--	180	727	30	24.2	24

* For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment ($C^n \times t = k$); NAS [2008] provided an empirically estimated n of 1.4 for all time-scaling. Additional information on the calculation of duration adjusted concentrations can be found in NIOSH [2013].
† The derived value is the result of the adjusted 30-minute concentration divided by the composite uncertainty factor.
‡ Composite uncertainty factor to account for adjustment of LC_{50} values to LC_{01} values, use of lethal concentration threshold in animals, interspecies differences and human variability.
§ Identified study is the primary basis of the IDLH value for ethylene dibromide.

4.0 Summary

The available data support the conclusion that the IDLH value should fall in the range of 24-48 ppm (see Table 4). The lowest LC_{50} of 200 ppm was reported in rats exposed for 12 hours [Rowe et al. 1952], however, further analysis of data from this study provided a calculation of an LCt_{50} for a 45-minute exposure resulting in a calculated LC_{50} of 800 ppm. This 45-minute LC_{50} of 800 ppm is the most appropriate IDLH value because it reduces the uncertainty associated with the duration adjustment to a 30-minute exposure. The LC_{50} value adjusted for a 30 minute exposure duration is 1069 ppm. Applying an uncertainty factor of 30 to account for extrapolation from a concentration that is lethal to animals, animal to human differences, and human variability results in an IDLH value of 36 ppm. Limited human data indicate that potentially escape-impairing effects (vomiting and respiratory discomfort) occur following exposure to 75 ppm ethylene dibromide during acute exposures [Ott 1980]. The derived IDLH value should also be protective of these severe and non-lethal, escape-impairing effects.
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